CENTER FOR DRUG EVALUATION AND RESEARCH

APPROVAL PACKAGE FOR:

APPLICATION NUMBER

21-184

Correspondence

DEPARTMENT OF HEALTH & HUMAN SERVICES Public Health Service

Food and Drug Administration
Rockville MD 20857

Division of Dermatologic and Dental Drug Products

Office of Drug Evaluation V
Center for Drug Evaluation and Research
Food and Drug Administration
9201 Corporate Boulevard, HFD-540
Rockville, MD 20850

FACSIMILE TRANSMISSION

DATE: January 18, 2000 Number of Pages (including cover sheet): 2

TO: Trudy A. Rumbaugh
COMPANY: Allergan
FAX #: 1-714-246-4292
MESSAGE: Please find comments from the Medical Reviewer for the NDA 21-184 Tazorac

Please provide a summary Table listing of the post-marketing events for Tazorac gels 0.05%, ———

FROM: Kalyani Bhatt
TITLE: Regulatory Project Manager
PHONE #: 301-827-2020
FAX #: 301-827-2075/2091

DEPARTMENT OF HEALTH & HUMAN SERVICES Public Health Service

Food and Drug Administration
Rockville MD 20857

Division of Dermatologic and Dental Drug Products

Office of Drug Evaluation V
Center for Drug Evaluation and Research
Food and Drug Administration
9201 Corporate Boulevard, HFD-540
Rockville, MD 20850

FACSIMILE TRANSMISSION

DATE: November 4, 1999 Number of Pages (including cover sheet) - 2

TO: Trudy A. Rumbaugh
COMPANY: Allergan
FAX #: 1-714-246-4272
MESSAGE: Please find comments from the Medical Reviewer for the NDA 21-184 Tazorac

FROM: Kalyani Bhatt
TITLE: Regulatory Project Manager
PHONE #: 301-827-2020
FAX #: 301-827-2075/2091

The medical reviewer has requested the following information:

1. Electronic documents in WORD or Wordperfect -
   Draft label
   Study reports of 190168-016C and 190168-017C
   Integrated Summary of Efficacy
   Integrated Summary of Safety
   Integrated Summary of Risk/benefit

2. p-values for adverse event data contrasting
   tazarotene 0.1% cream vs vehicle cream
   tazarotene 0.1% cream vs tazarotene 0.05% cream
   tazarotene 0.05% cream vs vehicle cream
   [ALL adverse events and treatment-related adverse events]

THIS SECTION WAS DETERMINED **NOT** TO BE RELEASABLE

2 pages

3. DDMAC Review of Patient Package Insert (PPI)

3.1. Issue. The proposed label for tazarotene creams includes a PPI. Ms. Karen Lechter of DDMAC reviewed the PPI and provided comments.

3.2. Background. It is the current policy of the Center that all proposed MedGuides and PPIs be reviewed by DDMAC.

3.3. Observations and Analyses.

3.3.1. Changes by Ms. Lechter.

- created headings and an order consistent with recommendations DDMAC makes for all current PPI's;
- reorganized material to fit into appropriate sections with the most important information first;
- removed inactive ingredients; [*The DDMAC version asks the patient not to use the product if "you are allergic to the ingredients in TAZORAC. The active ingredient is tazarotene. Ask your doctor or pharmacist about the inactive ingredients." It would be more convenient to the consumer to have the excipients listed in the PPI.*]
- eliminated the phrase [redacted]", but indicating in the beginning of the PPI that it does not take the place of discussions with the doctor. [*The only places with this phrase pertain to complete sunlamp avoidance. The physician may prescribe UV therapy in conjunction with tazarotene for psoriasis. Although this practice is not in the label, elimination of this phrase potentially casts doubt on the physician's judgment.*]

3.3.2. Questions by Ms Lechter.

3.3.2.1. Vitamin A. [redacted]

in other appropriate sections with some explanation about them. In the PI, there is only a mention that ingesting Tazorac can result in symptoms similar to Vitamin A overdose.

- Should the advice to tell a doctor about Vitamin A use be left out, or
- Should it be in the section on what to avoid while using Tazorac, or
- Should it be in the section about who should not use the product?
- If it is left in, what should it say?

Answer: The patient should tell the prescriber about Vitamin A usage, including its dose. The decision should depend on the judgment of the prescriber.

3.3.2.2. Products to be Used Carefully while Using Tazorac. In the section on what to avoid while using Tazorac, the second bullet contains a list of products to be used carefully while using Tazorac but not mentioned in the PI.

- The review division should examine the list to be sure the items are appropriate for inclusion in the second bullet.

Answer: Appropriate and may be included.

[redacted]

Answer: Stinging and burning are related sensations. Suggest replacing "[redacted]" alone with "burning or stinging". Concur that the statement that reactions may be less often as skin gets used to the drug can be left out, unless the Applicant can substantiate this with data.

3.3.2.4. Statement that Effectiveness with Less Than Once-a-Day Use Has not been Proven. Ms Lechter left out this statement, which was in the section indicating that the doctor may change the dosing of the medicine if side effects become a problem, as it may distress patients if dosing is reduced due to side effects.

- If the review division wants to retain this sentence, Ms Lechter recommends it be the last sentence in the first paragraph under "What are the possible side effects of TAZORAC?" to read: "However, effectiveness of TAZORAC when used less often than once a day has not been proven."

Answer: The statement may be retained at the end of the paragraph under "What are the possible side effects of TAZORAC?"

3.3.2.5. Storage Information. The PPI indicates that "excursions" from the normal storage temperature are permitted.

- To be useful, the PPI should specify how long the medication can be kept at more extreme temperatures. Ms Lechter left a blank in the text on this time.

Answer: This question should be addressed by the Chemistry Reviewer.

3.3.2.6. Reference to the National Psoriasis Foundation.

- Is it appropriate to have a reference to the NPF in the PPI?

Answer: Appropriate. The NPF may provide valuable information to patients.

3.3.2.7. Information for Patients Subsection of the PI.

- It is not sufficient, as it is now written, to refer the prescriber to the attached PPI, as we cannot be sure that the PPI will always be attached to the PI.

Answer: The PPI is always attached to the PI until cut out by the Pharmacist.

*The label has the following wording before the PPI: **"Pharmacist: Please cut or tear at dotted line and provide this patient package insert to your customer."** Thus, the prescriber's PI always includes the PPI. Moreover, the key precautionary elements have been provided under the "General" subsection immediately preceding the "Information for Patients" subsection.*

3.3.3. Revision of the Proposed PPI by DDMAC.

The following is the revised version of the proposed PPI for tazarotene creams by DDMAC:

INFORMATION FOR PATIENTS

[redacted]

Number of Pages Redacted 3

❖❖❖

Draft Labeling
(not releasable

DEPARTMENT OF HEALTH AND HUMAN SERVICES PUBLIC HEALTH SERVICE FOOD AND DRUG ADMINISTRATION	**REQUEST FOR CONSULTATION**

TO (*Division/Office*): DDMAC/HFD-42/Chuy/Rebecca			FROM: /S/ X72049 1. HFD-540	
DATE 2-22-00	IND NO.	NDA NO. 21-184	TYPE OF DOCUMENT	DATE OF DOCUMENT
NAME OF DRUG Tazorac	PRIORITY CONSIDERATION		CLASSIFICATION OF DRUG	DESIRED COMPLETION DATE 7/31/2000
NAME OF FIRM: ALLERGAN				

REASON FOR REQUEST

I. GENERAL

- ☐ NEW PROTOCOL
- ☐ PROGRESS REPORT
- ☐ NEW CORRESPONDENCE
- ☒ DRUG ADVERTISING
- ☐ ADVERSE REACTION REPORT
- ☐ MANUFACTURING CHANGE/ADDITION
- ☐ MEETING PLANNED BY
- ☐ PRE–NDA MEETING
- ☐ END OF PHASE II MEETING
- ☐ RESUBMISSION
- ☐ SAFETY/EFFICACY
- ☐ PAPER NDA
- ☐ CONTROL SUPPLEMENT
- ☐ RESPONSE TO DEFICIENCY LETTER
- ☐ FINAL PRINTED LABELING
- ☐ LABELING REVISION
- ☐ ORIGINAL NEW CORRESPONDENCE
- ☐ FORMULATIVE REVIEW
- ☐ OTHER *(SPECIFY BELOW)*:

II. BIOMETRICS

STATISTICAL EVALUATION BRANCH	STATISTICAL APPLICATION BRANCH
TYPE A OR B NDA REVIEW ID OF PHASE II MEETING ONTROLLED STUDIES ☐ PROTOCOL REVIEW ☐ OTHER (SPECIFY BELOW):	☐ CHEMISTRY REVIEW ☐ PHARMACOLOGY ☐ BIOPHARMACEUTICS ☐ OTHER (SPECIFY BELOW):

III. BIOPHARMACEUTICS

- ☐ DISSOLUTION
- ☐ BIOAVAILABILTY STUDIES
- ☐ PHASE IV STUDIES
- ☐ DEFICIENCY LETTER RESPONSE
- ☐ PROTOCOL-BIOPHARMACEUTICS
- ☐ IN-VIVO WAIVER REQUEST

IV. DRUG EXPERIENCE

- ☐ PHASE IV SURVEILLANCE/EPIDEMIOLOGY PROTOCOL
- ☐ DRUG USE e.g. POPULATION EXPOSURE, ASSOCIATED DIAGNOSES
- ☐ CASE REPORTS OF SPECIFIC REACTIONS (List below)
- ☐ COMPARATIVE RISK ASSESSMENT ON GENERIC DRUG GROUP
- ☐ REVIEW OF MARKETING EXPERIENCE, DRUG USE AND SAFETY
- ☐ SUMMARY OF ADVERSE EXPERIENCE
- ☐ POISION RICK ANALYSIS

V. SCIENTIFIC INVESTIGATIONS

☐ CLINICAL	☐ PRECLINICAL

COMMENTS/SPECIAL INSTRUCTIONS:

Please review labeling, carton, packaging.
If you have any question please call me. X72049.
/S/

SIGNATURE OF REQUESTER /S/	METHOD OF DELIVERY (Check one) ☐ MAIL ☐ HAND
SIGNATURE OF RECEIVER	SIGNATURE OF DELIVERER

MEMORANDUM

DEPARTMENT OF HEALTH AND HUMAN SERVICES

PUBLIC HEALTH SERVICE

FOOD AND DRUG ADMINISTRATION

CENTER FOR DRUG EVALUATION AND RESEARCH

DATE: JUL 24 2000

FROM: Allen Brinker, M.D., M.S., Epidemiologist AB 24Jly00

THROUGH: Julie Beitz, M.D. /S/ 7-24-00
Division Director
Office of Postmarketing Drug Risk Assessment II, HFD-430

TO: Jonathen Wilkin, M.D.
Director
Division of Dermatologic Drug Products, HFD-540

NDA: 21-184

PID#: D000533

SUBJECT: **Tazarotene and human teratogenicity**

EXCECUTIVE SUMMARY

In contrast to known human teratogens such as isotretinoin and thalidomide, data are lacking to characterize the effects of exposure of tazarotene on human pregnancies. From the point of view of the FDA, the strength of the animal studies suggests initiation of a Tazarotene Exposure Cohort with [redacted] The sponsor may conclude that the strength of the animal data mandates a Tazarotene Pregnancy Prevention Program. Both of these initiatives represent a substantial commitment of resources by the sponsor. A third option includes study through Teratogen Information Services. With concern over the potential human teratogenic effects, the tazarotene cream label should include an educational package for both patients and physicians on the teratogenic potential of tazarotene.

INTRODUCTION

This brief memorandum is based on the subsection of the Tazorac Topical **Cream** (NDA-21-184) review entitled [redacted]

BACKGROUND

As noted in the subsection of the medical officer's review supplied with the consult request, and by inspection of the label for Tazorac Topical **Gel**, teratogenic effects have been documented with the topical use of the active compound (tazarotene) in animals. Furthermore, as stated in the medical officer's review, topical tazarotene may lead to systemic exposure levels equivalent to those associated with teratogenicity in animals. This information lead to Pregnancy Category X designation for Tazorac Gel at the time of approval (Spring 1997). As the approval date precedes the release of the *FDA Guidance for industry. Establishing Pregnancy Registries* (released as **DRAFT** in June 1999), concepts, characteristics, and requirements for such programs were not available for HFD-540 or the drug sponsor at that time. In the interim, substantial progress has been made on both the content and implementation of the *Guidance* document.

OPTIONS FOR CONSIDERATION

We believe that the Guidance document does apply to Tazorac Topical Cream as it will be used by women of reproductive potential and it carries substantial **human** teratogenic concern. This choice of words has been specific as there are good data to support human teratogenic concern but actual human terotogenicity has not been shown to date. In general, these data can be used to suggest one of three possible paradigms for further study.

1. As the data to date do not include actual human teratogenicity, it is ethically acceptable to discourage pregnancy during conduct of a **Tazorac Exposure Cohort** [redacted]
   This was (apparently) the FDA position at approval for Tazorac Gel and remains a scientifically and ethically valid position for Tazorac Cream. As there was substantial concern for potential human teratogenicity at approval of tazarotene gel, tazarotene cream is NOT a candidate for a spontaneous [redacted] as currently in place for numerous anti-HIV agents. [In general, these agents did not induce observable teratogenice effects in lab animals and have been categorized as Pregnancy Class C agents.] These registries collect an uncertain fraction of pregnancies from an exposed population of unknown size via a 1-800-telephone line. Thus, for a robust study of human teratogenicity, it is imperative that representative and complete data be

collected. It would be anticipated that any Tazorac Exposure Cohort [redacted] would include both formulations.

As noted, the foundation for this program is a [redacted]. At the present time, there are no such ***observational*** programs in place. The clozapine (Clozaril) program includes registration of physicians, pharmacists, and patients for the purposes of mandatory hematological monitoring. [redacted]

2. If, based on current data, the drug sponsor believes concern for unproven human teratogenicity precludes **any** exposure during pregnancy, then the sponsor may support a **Tazorac Pregnancy Prevention Program**. In general, the creation of a pregnancy prevention program is more involved than an exposure registry with follow-up for pregnancy. Pregnancy prevention programs to date include registration of physician, pharmacy, and patient, comprehensive physician and patient education components, **mandatory pregnancy testing ("no blood, no drug")**, capture of complete outcome information from those women who become pregnant, and methods to assess the program's performance. Such a program could be modeled on the STEPS program in place for thalidomide. Selected requirements (DRAFT – FDA only) for a pregnancy prevention program are outlined on the attached table alongside the current STEPS program.

3. **Teratogen Information Services [TIS]** consists of investigators who collect information from poison control centers on spontaneous exposures. This organization has been used to evaluate human teratogenic potential.[1] As with either of the above routes of study, any TIS protocol must be prospectively approved through the reviewing division. [This option might represent a compromise given the unique position of this agent (see DISCUSSION)].

DICUSSION

As noted in discussion with HFD-540, implementation of any specific program to evaluate human teratogenicity with Tazorac cream is problematic as this information was apparently not required upon approval of topical tretinoin, adapalene, or tazarotene gel. This leads to the suggestion of TIS. In reference 1, Martinez-Frias and Rodriguez-Pinilla note that TIS data are imperfect (i.e. potentially biased) and suggest that it be used for generating hypotheses. However, there may be a role for the TIS in this situation. Given the relatively limited number of human pregnancies exposed to topical retinoids, collection of information from all of these agents would increase study power and potential.

CONCLUSION

In contrast to known human teratogens such as isotretinoin and thalidomide, data are lacking to characterize the effects of exposure of tazarotene on human pregnancies. From the point of view of the FDA, the strength of the animal studies suggests initiation of a Tazarotene Exposure Cohort with [redacted]. The sponsor may conclude that the strength of the animal data mandates a Tazarotene Pregnancy Prevention Program. Both of these initiatives represent a substantial commitment of resources by the sponsor. A third option includes study through Teratogen Information Services. With concern over the potential human teratogenic effects, the tazarotene cream label should include an educational package for both patients and physicians on the teratogenic potential of tazarotene.

REFERENCES

1. Martinez-Frias M.L., Rodriguez-Pinilla E. Problems of using data from Teratology Information Services (TIS) to identify putative teratogens. Teratology 1999;60:54-5.

cc:

HFD-540//Wilkin/Kozma-Fornaro/Bhatt

HFD-400//Honig

HFD-430//Beitz / Trontell / Chen / Brinker

NDA File # 20-903

Division file

DEPARTMENT OF HEALTH AND HUMAN SERVICES PUBLIC HEALTH SERVICE FOOD AND DRUG ADMINISTRATION	**REQUEST FOR CONSULTATION**

TO *(Division/Office)*:OPDRA/ PATRICK GUINN	FROM:KALYANI BHATT, PROJECT MANAGER HFD-540 301-827-2049

DATE	IND NO.	NDA NO.	TYPE OF DOCUMENT	DATE OF DOCUMENT
7-12-00		21-184		

NAME OF DRUG	PRIORITY CONSIDERATION	CLASSIFICATION OF DRUG	DESIRED COMPLETION DATE
TAZORAC tazarotene(0.05% [redacted] Topical Creme		acetylenic retinoid	JULY 26, 2000

NAME OF FIRM: ALLERGAN 2525 DUPONT DRIVE, P.O. BOX 19534, IRVINE, CA 92623-9534 1-714-246-4470

REASON FOR REQUEST

I. GENERAL

- ☐ NEW PROTOCOL
- ☐ PROGRESS REPORT
- ☐ NEW CORRESPONDENCE
- ☐ DRUG ADVERTISING
- ☐ ADVERSE REACTION REPORT
- ☐ MANUFACTURING CHANGE/ADDITION
- ☐ MEETING PLANNED BY
- ☐ PRE--NDA MEETING
- ☐ END OF PHASE II MEETING
- ☐ RESUBMISSION
- ☐ SAFETY/EFFICACY
- ☐ PAPER NDA
- ☐ CONTROL SUPPLEMENT
- ☐ RESPONSE TO DEFICIENCY LETTER
- ☐ FINAL PRINTED LABELING
- ☐ LABELING REVISION
- ☐ ORIGINAL NEW CORRESPONDENCE
- ☐ FORMULATIVE REVIEW
- ☐ OTHER *(SPECIFY BELOW)*:

II. BIOMETRICS

STATISTICAL EVALUATION BRANCH	STATISTICAL APPLICATION BRANCH
☐ TYPE A OR B NDA REVIEW ☐ END OF PHASE II MEETING ☐ CONTROLLED STUDIES ☐ PROTOCOL REVIEW ☐ OTHER (SPECIFY BELOW):	☐ CHEMISTRY REVIEW ☐ PHARMACOLOGY ☐ BIOPHARMACEUTICS ☐ OTHER (SPECIFY BELOW):

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- ☐ PROTOCOL-BIOPHARMACEUTICS
- ☐ IN-VIVO WAIVER REQUEST

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- ☐ POISION RICK ANALYSIS

V. SCIENTIFIC INVESTIGATIONS

- ☐ CLINICAL
- ☐ PRECLINICAL

Tazorac (tazarotene) 0.05% & [redacted] Topical Cream is a pending NDA for the treatment for Plaque Psoriasis. This is retinoid NDA 21-184; Tazorac gel is approved for acne and plaque psoriasis. Please provide advice /recommendation for a pregnancy registry for topical use of tazarotene products.

SIGNATURE OF REQUESTER Kalyani Bhatt, HFD-540, 301-827-2049	METHOD OF DELIVERY (Check one) ☐ MAIL ☐ HAND
SIGNATURE OF RECEIVER	SIGNATURE OF DELIVERER

Electronic Mail Message

Date: 3/27/00 3:23:33 PM
From: Jerry Phillips (PHILLIPSJ)
To: Kalyani Bhatt (BHATTK)
Cc: Sammie Beam (BEAMS)
Cc: Peter Honig (HONIGP)
Subject: 2/18/99 Consult for TAZORAC (OPDRA 00-0082)

Kalyani:

Please consider this an official response from OPDRA concerning your consult dated 2/18/00 for a proprietary name review of TAZORAC for a new cream formulation for tazarotene. Since TAZORAC is an approved proprietary name for their gel formulation, OPDRA has no objection to the firm's proposal to use the same name for their cream formulation. If you have any questions, please feel free to call me at 827-3246. Thanks!

Jerry Phillips
Associate Director, OPDRA

APPEARS THIS WAY
ON ORIGINAL

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION

REQUEST FOR CONSULTATION

TO *(Division/Office)*: OPDRA HFD-400, Rm 15B03 Sammie Beam, Project Manager

FROM: Kalyani Bhatt, Project Manger HFD-540

2-18-99	IND NO.	NDA NO. 21-184	DATE OF DOCUMENT

NAME OF DRUG	PRIORITY CONSIDERATION	CLASSIFICATION OF DRUG	DESIRED COMPLETION DATE
Tazorac (tazarotene 0.05% & 0.1%)			July 31, 2000 (10-month user fee date)

NAME OF FIRM: ALLERGAN

REASION FOR REQUEST

I. GENERAL

- ☐ NEW PROTOCOL
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- ☐ PHASE IV STUDIES
- ☐ DEFICIENCY LETTER RESPONSE
- ☐ PROTOCOL-BIOPHARMACEUTICS
- ☐ IN-VIVO WAIVER REQUEST

IV. DRUG EXPERIENCE

- ☐ PHASE IV SURVEILLANCE/EPIDEMIOLOGY PROTOCOL
- ☐ DRUG USE e.g. POPULATION EXPOSURE, ASSOCIATED DIAGNOSES
- ☐ CASE REPORTS OF SPECIFIC REACTIONS (List below)
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- ☐ REVIEW OF MARKETING EXPERIENCE, DRUG USE AND SAFETY
- ☐ SUMMARY OF ADVERSE EXPERIENCE
- ☐ POISION RICK ANALYSIS

V. SCIENTIFIC INVESTIGATIONS

- ☐ CLINICAL
- ☐ PRECLINICAL

Requested from sponsor carton, labeling on 2-18-00 which I will forward to you.

Sent consult on 2-23-00.

TURE OF REQUESTER Kalyani Bhatt HFD-540 827-2049	METHOD OF DELIVERY (Check one) ☐ MAIL ☐ HAND
SIGNATURE OF RECEIVER	SIGNATURE OF DELIVERER

BEST POSSIBLE COPY

Palynzi

NDA ACKNOWLEDGEMENT LETTER

NDA 21-184

Acknowledgement letter went out.

Firm Name Allergan, Inc

Contact Trudy A. Rumbaugh, MD,

Contact Title Director, Global Regulatory Affairs

Address 2525 Dupont Drive

P.O. Box 19534

Irvine, CA 92623-9534

714 246-4292

FAX

714, 246-4272

Tom Walton - 246. - x4470

Dear Dr. Rumbaugh

Name of Drug (Trade/Generic/Dosage Form): Tazorac (tazarotene) 0.05%/0.1%

Topical Cream

Therapeutic Classification: 3S

File Date November 29, 1999

Date of Application: September 30, 1999

Primary User Fee Goal Date (10 mos) July 31, 2000

Date of Receipt September 30, 1999

Secondary User Fee Goal Date (12 mos)

User Fee: Received yes Not required _____ Not received _____

Firm in arrears for other fees No

Review Information:

New Molecular Entity? No

Subpart H (accelerated review)? No

Subject to AIP (Application Integrity Policy)? No

Project Manager /S/

Subject: TAZORAC Cream/NDA 21-184

Title/Date: Allergan/FDA Teleconference: August 29, 2000

Attendees: FDA: J. Wilkin, K. Bhatt, W. Timmer
AGN: P. Kresel, J. Gibson, P. Walker, J. Sefton, D. Tang-[illegible]u, B. Brar, T. Rumbaugh, T. Walton

Subjects: Draft Labeling, Chemistry, Manufacturing and Controls and Pregnancy Data Collection

Key Agreements and Decisions:

- Draft Labeling:

Allergan has received the Draft Labeling from FDA and is performing an internal review of the label and committed to returning the Draft to FDA with Allergan's comments within a very short time.

Post-meeting note: Allergan completed the internal review and forwarded the Draft Label with our comments to FDA on August 30 by e-mail.

I confirmed by telephone the receipt of the Draft Label.

FDA has requested an unannotated copy of the Draft Label (August 31).

- Chemistry, Manufacturing and Controls:

FDA has requested a Phase 4, Photostability study of TAZORAC Cream .1% that exposes the drug product to a [redacted]

Allergan agreed to follow-up by letter to FDA on the test protocol to be followed and the timeframe for completion.

Post-meeting note: Allergan forwarded to FDA the Final Report for PA-1999-156, a photostability study that was performed utilizing Taz Crm 0.1% and the ICH Guideline recommendations for photostability. This report was contained in the NDA. FDA was asked to identify any chemistry or regulatory shortcomings of the study in order to optimize the Phase 4 study.

I confirmed by telephone the receipt of the report and the request for FDA feedback.

- Pregnancy Data Collection Protocol:

Due to the limitations of the Pregnancy Category classifications in the CFR, FDA has requested that Allergan prospectively identify women who inadvertently become pregnant while on TAZORAC Cream therapy in order to build a database on such exposure.

This data would eventually be included in the labeling to help women and their doctors make informed decisions and would be presented in a fashion that would not encourage exposure.

Allergan has proposed [redacted]

Teleconference Date: August 29, 2000 Time: 1500 Location: N225

NDA 21-184, Tazorac (tazarotene topical cream) Cream, 0.05%, 0.1%

Indications: Topical Treatment of Plaque Psoriasis

Sponsor: Allergan, Inc.

Purpose of Meeting: Guidance Meeting

Meeting Chair: Jonathan K. Wilkin, M.D.

Meeting Recorder (CSO/Project Manager): Frank H. Cross, Jr., M.A., CDR

FDA Attendees, titles and offices:

Jonathan K. Wilkin, M.D., Division Director, DDDDP, HFD-540
Frank H. Cross, Jr., M.A., CDR, Senior Regulatory Management Officer, DDDDP, HFD-540

Sponsor Attendees, titles and offices:

Peter Kresel, Vice President, Regulatory Affairs
Trudy Rumbaugh, M.D., Director, Global Regulatory Affairs, Retinoids
Thomas Walton, Specialist, Regulatory Affairs

In response to the Applicant's request for feedback on progress of the NDA review, the Agency had the following discussion:

Agency:

The Agency reiterated to the Applicant the primary and secondary goal dates for the NDA. In addition, the Agency said that it would share its proposed labeling for this NDA as soon as possible. Finally, the Agency informed the Applicant that a [redacted] may be requested for this NDA.

Applicant:

The Applicant appreciated our feedback and looks forward to future interactions and discussions of the proposed labeling and the topic of a [redacted] for this drug.

The teleconference ended amicably.

/S/

Signature, minutes preparer: _____

Concurrence Chair (or designated signatory): _____

cc:

NDA 21-184
HFD-540
HFD-540/DIV DIR/Wilkin
HFD-540/CHEM TL/DeCamp
HFD-540/CHEM/Hathaway
HFD-540/CHEM/Timmer
HFD-540/PHARM TOX TL/Jacobs
HFD-540/PHARM TOX/Nostrandt
HFD-880/BIOPHARM TL/Bashaw
HFD-880/BIOPHARM/Lee
HFD-540/DERM TL/Walker
HFD-540/MO/Ko
HFD-725/ACT BIOSTAT TL/Al-Osh
HFD-880/BIOSTAT/Lee
HFD-540/PM/Cross
HFD-540/PM/Bhatt
Drafted by: fhc/September 21, 2000
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Initialed by:
final:

MEMORANDUM OF TELECONFERENCE

DEPARTMENT OF HEALTH & HUMAN SERVICES

Kalyani

Food and Drug Administration
Rockville MD 20857

APR 24 2000

J. Michael Maloney, M.D.
3535 Cherry Creek North Drive, #207
Denver, Colorado 80209

Dear Dr. Maloney:

Between February 14 and 16, 2000, Ms. Grace E. McNally and Ms. Patricia Cortez, representing the Food and Drug Administration (FDA), met with you and your staff to review your conduct of a clinical study (protocol #190168-016C-00) of the investigational drug Tazorac (tazarotene topical cream 0.025%, 0.05% and 0.1%), performed for Allergan. This inspection is a part of FDA's Bioresearch Monitoring Program, which includes inspections designed to validate clinical studies on which drug approval may be based and to assure that the rights and welfare of the human subjects of those studies have been protected.

From our evaluation of the inspection report and the documents submitted with that report, we conclude that you adhered to all pertinent federal regulations and/or good clinical investigational practices governing your conduct of clinical investigations and the protection of human subjects.

We appreciate the cooperation shown our personnel during the inspection. Should you have any questions or concerns about any aspect of the clinical testing of investigational drugs, please contact me at (301)594-1032.

Sincerely,

/S/

Antoine El-Hage, Ph.D.
Branch Chief
Good Clinical Practice II, HFD-47
Division of Scientific Investigations
Office of Medical Policy
Center for Drug Evaluation and Research
7520 Standish Place
Rockville, MD 20855

CFN: 3002946108

Field Classification: NAI

Headquarters Classification:
__X__1) NAI
_____ 2) VAI-no response required
_____ 3) VAI-response requested

If Headquarters classification is a different classification, explain why:

cc:
HFA-224
HFD-540 Review Div. Dir.
HFD-540/ MO/Ko
HFD-540/ PM/Kalyani
HFD-540/Doc. Rm. NDA # 21-184
HFD-45 r/f
HFD-47 c/r/s GCP file# 10016
HFD-47/Carreras
HFD-47/Currier
HFR-SW250/Singleton
HFR-SW250/Sherer
HER-SW250/McNally

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Note to Rev. Div. M.O.

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service
Food and Drug Administration

Memorandum

Date September 25, 2000

From William C. Timmer, Ph.D. /S/ WD 9/26/00

Subject Labeling of **NDA 20-600** Tazorac® Gel and **NDA 21-184** Tazorac® Cream

To Jonathan K. Wilkin, M.D. /S/ 9/27/00

Regarding NDA 20-600 Tazorac Gel:

A review of the sponsor' most recent annual report, dated 10-NOV-99, has shown that the label for this drug product is written as:

TAZORAC®
(tazarotene gel) Topical Gel, 0.1%, 0.05%

The carton label is:

This is incorrect. According to 21 CFR 201.10(g)(1), the established name should be placed in direct conjunction with the proprietary name. Moreover, §299.4(d) indicates that the FDA follows the USAN convention. The USAN USP Dictionary contains a listing for tazarotene. Therefore, the only term within the parenthesis should be tazarotene.

Accordingly, it is recommended that the sponsor promptly remove the term gel from within the parenthesis [within 6 months; preferably sooner].

In order to remove any ambiguities, the labeling for ALL tazarotene products should be

similar to:

TAZORAC®
(tazarotene) Dosage Form, Concentration

If a USP monograph for tazarotene gel or cream is approved, then the term gel or cream may be inserted between the parenthesis. This change may be effected via an annual report.

Regarding NDA 21-184 Tazorac Cream:

As noted in Chemistry Review #1, the phrase topical cream should be eliminated from within the parenthesis, again leaving only tazarotene within the parenthesis.

Summary:

Regardless of whether the dosage form is cream or gel, the labeling needs to be correct and consistent with the appropriate regulations.

tember 27, 2000

athan K. Wilkin, MD
ctor, Division of Dermatological and Dental Drug Products (HFD-540)
iter for Drug Evaluation & Research
d and Drug Administration
ument Control Room
1 Corporate Boulevard
kville, MD 20850

BB

NDA 50-781
Minocycline PTS
Amendment: Biopharmaceutics Requested Information

ir Dr. Wilkin:

erence is made to telefax received on September 20, 2000 requesting additional rmation for the Biopharmaceutics Reviewer.

s idment provides information / data to the FDA questions or request. I have d each point separately followed by our response.

ou have any questions regarding this submission, please contact me at [redacted]

cerely,

/S/

cutive Director, Regulatory Affairs and Quality Assurance

m FDA 356h
omitted in duplicate

Question 1
Question 2
Question 3
Question 4
Attachment 1

BEST POSSIBLE COPY

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Dupont Drive, P.O. Box 19534, Irvine, California, USA 92623-9534 Telephone: (714) 246-4500 Website: www.allergan.com

50 years GROWTH & INNOVATION

September 13, 2000

NDA CDIC AMENDMENT

Jonathan Wilkin, MD
Director,
Division of Dermatologic and Dental Drug Products
HFD-540/Room N115
Center for Drug Evaluation and Research
Food and Drug Administration
9201 Corporate Blvd., Building 2
Rockville, MD 20850

REF: TAZORAC® (tazarotene) Cream 0.05%, 0.1%
NDA 21-184
Response to receipt of Draft Labeling

BL

Dear Doctor Wilkin:

Allergan is amending the above-referenced NDA with a response to the Draft Labeling received from your Division on September 8, 2000. Allergan is accepting the Labeling as received.

We understand that the issue of the nomenclature for expression of the tradename/generic name is still to be settled following additional internal discussion within FDA. We should like to point out that you have presented in the Draft Labeling two different expressions of the tradename/generic name. On the title page of the Label (page 1 of 12) TAZORAC is presented as TAZORAC® (tazarotene) Cream, 0.05% and 0.1% and in the Information for Patients (Page 10 of 12) it is presented as TAZORAC® (tazarotene topical cream) 0.05% and 0.1%. This latter presentation is consistent with how TAZORAC® Gel is expressed and is our preference.

In any event, in accordance with our discussions with you on Monday, September 11, 2000, Allergan will be permitted to utilize our printed materials decorated as TAZORAC® (tazarotene topical cream) 0.05% and 0.1%. When FDA makes final its decision on the tradename/generic name, Allergan will modify all printed materials in accordance with that decision.

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pont Drive, P.O. Box 19534, Irvine, California, USA 92623-9534 Telephone: (714) 246-4500 Website: www.allergan.com

50 years
GROWTH & INNOVATION

September 1, 2000

NDA DRUG AMENDMENT

Jonathan Wilkin, MD
Director,
Division of Dermatologic and Dental Drug Products
HFD-540/Room N115
Center for Drug Evaluation and Research
Food and Drug Administration
9201 Corporate Blvd., Building 2
Rockville, MD 20850

BL

REF: TAZORAC® (tazarotene topical cream) 0.05%, 0.1%
NDA 21-184
Submission of Annotated and Non-annotated Draft Labeling

Doctor Wilkin:

Allergan is amending the above-referenced NDA with a submission of Draft Labeling previously sent to the Project Manager by electronic mail.

We ask that this Draft Labeling be reviewed and filed to NDA 21-184, TAZORAC® Cream, 0.05%, 0.1%. Should you require further information or have any additional requests please call me at 714.246.4292 or Thomas Walton at 714.246.4470, Pacific Time.

Sincerely,

Trudy A. Rumbaugh, MD
Director,
Global Regulatory Affairs, Retinoids

TR/tww

CENTER FOR DRUG
REC'D
SEP 05 2000
MEGA DOC RM
EVALUATION AND RESEARCH

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Annotated

ALLERGAN

2525 Dupont Drive, P.O. Box 19534, Irvine, California, USA 92623-9534 Telephone: (714) 246-4500 Website: www.allergan.com

50 years GROWTH & INNOVATION

July 27, 2000

Jonathan Wilkin, MD
Director,
Division of Dermatologic and Dental Drug Products
HFD-540/Room N115
Center for Drug Evaluation and Research
Food and Drug Administration
9201 Corporate Blvd., Building 2
Rockville, MD 20850

REF: TAZORAC® (tazarotene topical cream) 0.05%, 0.1%
NDA 21-184
Response to FDA Fax of July 24, 2000

Dear Doctor Wilkin:

Allergan is amending the above-referenced NDA with a response to an FDA Pharmacology-Toxicology request for clarification of study results.

FDA Request for Clarification

Clarification is requested for study TX99008. The ophthalmology reports are identical for animals 302 and 351. Both have a set of lesions that are unlikely to be exactly duplicated. Please recheck the ophthalmology reports for all animals in the study.

Allergan Response

The ophthalmoscopy reports referenced above (located in Appendix IX) are written as shown below:

Animal number 302, male rat in Group 3 (0.05% tazarotene cream containing 0.1% ascorbic acid): *"OU Cornea Appear Cloudy at 3:00 OD and 9:00 OS, No other findings."*

Animal number 351, female rat in Group 3 (0.05% tazarotene cream containing 0.1% ascorbic acid): *"Both Cornea Appear Cloudy (Opacity) at 9:00 OS and 3:00 OD, No other findings."*

The accuracy of these statements was confirmed by comparison to the raw ophthalmoscopy data for the study. Furthermore, the data for all animals in Appendix IX of the report were compared to the raw ophthalmoscopy data for the study. In all cases, the ophthalmoscopy findings summarized in Appendix IX accurately reflect the raw data collected for the study.

Response to FDA Fax
Page 2 of 2

Therefore, the similarity of corneal lesions between the two above-referenced animals is a rare, but genuine coincidence.

The cloudy corneas observed in one of ten Group 3 males and one of ten Group 3 females were considered to be sporadic and not related to treatment with tazarotene. This is supported by the fact that cloudy corneas were not seen in Group 5 rats treated with the high concentration of the drug (0.1% tazarotene cream containing 0.1% ascorbic acid).

We ask that this response be reviewed and filed to NDA 21-184, TAZORAC® Cream. Should you have any further questions or require additional information, please call me at 714.246.4292 or Thomas Walton at 714/246.4470, Pacific Time.

Sincerely,

T. Rumbaugh M.D.

Trudy A. Rumbaugh, MD
Director,
Global Regulatory Affairs, Retinoids

TR/tww

APPEARS THIS WAY
ON ORIGINAL

...on: Drive, P.O. Box 19534, Irvine, California, USA 92623-9534 Telephone: (714) 246-4500 Website: www.allergan.com

50 years GROWTH & INNOVATION

June 7, 2000

NDA ORIG AMENDMENT

Jonathan Wilkin, MD
Director,
Division of Dermatologic and Dental Drug Products
HFD-540/Room N115
Center for Drug Evaluation and Research
Food and Drug Administration
9201 Corporate Blvd., Building 2
Rockville, MD 20850

REF: TAZORAC® (tazarotene topical cream) 0.05%, 0.1%
NDA 21-184
Response to May 17 Electronic Mail from Hon-Sum Ko, MD

BM

Dear Doctor Wilkin:

Allergan is amending the above-referenced NDA with a response to the Medical Reviewer's electronic mail message received by us on May 17, 2000.

Medical Reviewer:

There are some questions I need help on:

1. *The study reports for 190168-016C and 017C give incidence of laboratory adverse events. Since the definition of lab adverse event is simply checking "yes" on the case report form, it is impossible for me to sort out who has had a lab adverse event without further information. Could you give me a listing of these patients and their lab values considered as lab adverse events?*

Allergan:

For the 190168-016C study, a revised Table 67 (Page 1 of 2) is provided (no changes for Table 67 (Page 2 of 2). Within the vehicle group, two patients with laboratory adverse events were inadvertently omitted from this table in the September 30, 1999 submission. These patients were:

nt	Lab AE	Relationship to Treatment
-E09	Increased ALT, AST	Possible
2766-P25	Hematuria	None.

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herefore, there is one additional treatment-related lab AE and one treatment-unrelated AE. ttached is Listing 1 (treatment period) and 2 (post-treatment period) of reported laboratory dverse events. Laboratory values are presented in Listing 3 (hematology and blood chemistry) nd Listing 4 (urinalysis).

or the 190168-017C study, a revised Table 56 (Page 1 of 1) is provided. One patient-report of aboratory adverse events was inadvertently excluded from this table in the September 30, 1999 ubmission. This one patient was in the tazarotene 0.05% group.

ttached is Listing 5 of reported laboratory adverse events. Laboratory values are presented in isting 6 (hematology and blood chemistry) and Listing 7 (urinalysis).

ledical Reviewer:

There is a listing for the patients with abnormal laboratory findings (not laboratory adverse events). However, some of the patients with abnormal findings do not seem to be listed, e.g., 2167-E09. Could you tell what is excluded in this listing?

llergan:

able 71 (016C study) and Table 59 (017C study) list laboratory values that shifted from baseline follow-up. The values listed in these tables are those that changed from low to high (L → H), ormal to low (N → L), high to low (H → L), and normal to high (N → H). (L represents outside e lower limit of normal range; N represents within the normal limits, and H represents outside the pper limit of normal range.) Those laboratory values that were categorized as N → N, L → N, L L, H → N and H → H are not listed in Tables 71 and 59.

edical Reviewer:

The text for study report for 190168-016C differs from the Table with respect to the number of patients with possibly related laboratory adverse events in the vehicle arm during the treatment period. The Table says there was one patient, but the text says: "two patients in the vehicle group had possibly-related events: 1 patient had increased ALT and AST (2167-E09), and 1 patient had increased triglygerides (2766-P33)." Which is correct? I also note that this sentence is identical to the one used in the post-treatment period.

lergan:

ted in the response to Question #1, Table 67 (page 1 of 2) was revised. There was one atment-related Lab AE that was inadvertently omitted from this table in the earlier submission. is was patient 2167-E09 (increased ALT, AST).

With this one addition, the number of patients with treatment-related Lab AEs in the Vehicle group should correspond to the text of the final report (see response to Question #1).

As described in Listing 1 (pages 5 and 6 of 6), patients 2167-E09 and 2766-P33 experienced treatment-related lab AE(s) during the treatment period. As described in Listing 2 (pages 5 and 6 of 6), these same patients experienced the same treatment-related lab AE(s) during the post-treatment period.

Medical Reviewer:

4. *There are cases of allergic contact dermatitis in the above studies (at least one in each study), could you provide evidence that the contact dermatitis was allergic in nature?*

Allergan:

Of the 5 cases of allergic contact dermatitis that were reported (patients #H16, #J35, #R46 in Study '90168-016C; patients #B23 and #M49 in Study 190168-017C), the adverse events in all 5 cases ere described by the investigators as "poison ivy". At Allergan, the COSTART codes that are assigned for an investigator description of poison ivy is "DERM CONTACT ALLERGIC". None of the investigators felt that the poison ivy adverse events were treatment-related.

Medical Reviewer:

5. *In Study 190168-016C, patient 0188-N31 used medication from 5/6/98 to 6/26/98, but the listing says use of study drug for 36 days. Could you clarify the difference?*

Allergan:

1. The patient was hospitalized from 6/27/98 – 8/3/98 for pancreatitis; during that hospitalization the patient did not use the study medication.
2. The patient was exited from the study on 8/11/98 (discontinued due to AE).

From the above, one may arrive at the conclusion that the drug was taken from 5/6/98 to 6/26/98 (~52 days). This may be true or not true. The listing used the algorithm below and may underestimate the exposure time for that individual.

Exposure time (days) = date of last treatment visit – baseline date +1 (6/10/98 – 5/6/98 + 1)

We hope these response clarify the Medical Reviewer's understanding of the data. Should you have additional questions or require further information. please call me at 714.246.4292 or Thomas Walton at 714.246.4470, Pacific Time.

Sincerely,

Thomas Walton for

Trudy A. Rumbaugh, MD
Director,
Global Regulatory Affairs, Retinoids

TR/tww

...Drive, P.O. Box 19534, Irvine, California, USA 92623-9534 Telephone: (714) 246-4500 Website: www.allergan.com

50 years GROWTH & INNOVATION

May 15, 2000

NDA CMC AMENDMENT

Jonathan Wilkin, MD
Director,
Division of Dermatologic and Dental Drug Products
HFD-540/Room N115
Center for Drug Evaluation and Research
Food and Drug Administration
9201 Corporate Blvd; Building 2
Rockville, MD 20850

MAY 17 2000

BM

REF: TAZORAC® (tazarotene topical cream) 0.1%, 0.5%
NDA 21-184
Response to FDA Clinical E-mail Questions of April 24, 27 and 28, 2000

Dear Doctor Wilkin:

Allergan is amending the above-referenced NDA with a response to a request for clinical and statistical information and clarification received from Hon-Sum Ko, MD.

April 24:
Question 1

I don't understand the patient numbers for the interim visits for the efficacy Tables in section 14 for the intent-to-treat analysis. Since you use LOCF, the interim visits should all have the same number of patients as the initial and final visits. I see that the final visit at week 12 has the same patients numbers as the numbers enrolled. That is fine. However, the interim visits do not have the same numbers. I expect you have the same patient numbers for all visits because it is ITT and LOCF. Otherwise, you need to explain every number for who is being included! It may be easier to give me the the reall ITT with LOCF so that all visits have the same patient numbers.

Allergan Response:
Located in Section 16.1.9.2 of each study report is the statistical analysis plan (SAP). In the SAP for the 190168-017C study (as an example), section **4.13.2.1.1.1** presents the definition of intent-to-treat (ITT), and the conditions for carrying forward data. It reads:

> "An intent-to-treat (ITT) analysis will be performed on all efficacy variables. In this analysis, efficacy data from randomized patients will be included. Efficacy data will be carried forward (LOCF) for patients who discontinued (regardless of cause) from the study prior to week 12."

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The algorithm for carrying forward efficacy data is summarized as follows:

1. Efficacy data will be carried forward from the last visit.
2. If the last observation is missing, then data from the previous visit will be carried forward.
3. If two visits fall within a time window, then the last observation will be carried forward.

Criteria 2 and 3 are the exceptions to criteria # 1 which is the general rule.
In cases where there is no follow-up visit but only a baseline visit, data from the baseline visit will be carried forward. For the variable "response to treatment", since there is no baseline evaluation, a response of "condition unchanged" will be imputed.

Furthermore, Section **4.13.2.1.2** describes the treatment of missing visits or values:
Besides methods for imputing data by LOCF as described in section 4.13.2.1.1.1 and 4.13.2.1.1.2, there are no other methods for imputing data for missing observations. For example, for a patient who successfully completed the study but had a missed visit, or if the data is not recorded for various reasons, then this missing observation will be left missing.

Therefore, the interim visits do not have the same patient numbers as missed visits or values were not imputed.

Section **4.13.2.1.3** describes the visit tolerance windows. It is as follows:

Because not all patients will adhere to the protocol in terms of returning for follow-up visits on schedule, the following preliminary "time windows" will be assigned to a "nominal" week:

Treatment Period: Time Window (days)	Scheduled Day	Week
0	0	0
1-10	7	1
11-20	14	2
21-41	28	4
42-69	56	8
≥70	84	12

Therefore, given the above rules set forth in the SAP, efficacy data for a missed visit were not imputed. For example, suppose there are 10 patients with various follow-up outcomes as shown below:

Patient	Week 0	Week 1	Week 2	Week 4	Week 8	Week 12
1	X	X	X	X	X	X
2	X	X	M	X	X	X
3	X	D(locf)	D(locf)	D(locf)	D(locf)	D(locf)
4	X	X	M	X	X	X
5	X	X	M	X	X	D(locf)
6	X	M	X	X	M	X
7	X	X	X	X	X	X
8	X	X	M	XX	X	X
9	X	X	D(locf)	D(locf)	D(locf)	D(locf)
10	X	X	X	X	X	X
Number Of Patients Shown on Stat table	**N = 10**	**N = 9**	**N = 6**	**N = 10**	**N = 9**	**N = 10**

X = evaluable visit; D = drop-out qualifying for locf; M = missed visit; XX = 2 visits with efficacy data within the same time window. Visits with "M" will not have efficacy data.

For patient 3, data will be carried forward from Week 0. Patient 5 data will be carried forward from Week 8, but efficacy data will not be imputed for Week 2. Patient 9. data will be carried forward from Week 1. No data will be imputed for visits with a "M." With this in mind, the above N's are arrived at.

Question 2

For Study 016C, (a) could you please also attach a page for the complete information on the dropout reasons to me at your earliest convenience re: vol 18 page 089 (section 14.1, Table 1, page 2) on "other" exit reasons. Many of the sentences are incomplete. (b) When the item says HIGH LABS, could you also specify what lab parameter, and when (baseline or which week)? I would appreciate it.

Allergan Response:

(a) See accompanying table on following page.

(b) See "Attachment 1"

Attachment 1

Table 1 (Page 2 of 2)

Patient Exit Reason : Other
(Intent-to-Treat)

Treatment	Patient	Exit Reason	Comment
Taz 0.05%	A51	Other	PT. DIAGNOSED WITH HEPATITIS C ON DAY AFTER BL VISIT
	C13	Other	HIGH LABS
	M16	Other	ABNORMAL LABS HAD BEEN ELEVATED AT BEGINNING OF STUDY BUT STILL GOING UP
Taz 0.1%	A46	Other	ENLARGEMENT OF LESIONS. PT REQUESTS TERMINATION
	C27	Other	ASTHMA ATTACK WHICH REQUIRED PO STEROIDS
	C32	Other	HIGH LABS
	N11	Other	SPONSOR REQUESTED DC DUE TO ELEVATED TRIGLYCERIDES IN REPEATED B.L. LABS
	N27	Other	NON COMPLIANT WITH VISIT SCHEDULE
Vehicle	F41	Other	STUDY TERMINATED EARLY PI LEAVING PENN
	G17	Other	PERSONAL
	J12	Other	PT UNABLE TO OBTAIN MEDS FOR STUDY IN TIME TO CON'T
	J33	Other	ABNORMAL BASELINE LABS
	M02	Other	EVIDENCE OF LIVER DAMAGE AT START OF STUDY
	N16	Other	DISCONTINUED PER SPONSOR'S REQUEST. ELEVATED TRIGLYCERIDES AT REPEATED B.L. LAB

/bostat/lue_jo/190168016c/dispt.sas/01MAY00

Question 3:

For 017C, section 14.1, Table 1, page 2, the lines seem complete, but there is one patient where the discontinuation information is unclear. On patient A11 (tazarotene 0.1%), when was the patient discontinued? Was the elevated triglycerides a baseline finding or a change from baseline; if so, which week? For several other patients who were listed as having abnormal or elevated baseline labs, the abnormal parameters also need to be specified as discussed above for 016C.

Allergan Response:
See "Attachment 2."

Question 4:

For 017C, there is a Table 98 with Safety Data (vol 51, pp 281-2), which has no counterpart in 016C. Could you explain to me what this is about? What is "expanded ref range"? and why there are so few patients at baseline and even fewer at week 4, the only follow-up visit with data?

Allergan Response:
190168-017C was started before study 190168-016C. Shortly after the start of the 017C study and before the start of the 016C study, the central laboratory [redacted] changed the reference range for Urea Nitrogen/Creatinine Ratio. The change occurred on 2/5/98. The original reference range (before 2/5/98) was based on literature information, and the second one was from an internal study performed at [redacted]

Table 98 presents the data before the change. The old reference range applied to a small proportion of observations as shown on Table 98. Table 97 presents the data after the change. The new reference range applied to a larger proportion of observations as shown on this table. For the 016C study, the data reflects after the change for this parameter. That is why there is no table similar to the 017C Table 98 (expanded ref range).

FDA Question from April 27 E-mail:

In addition to the clarification and material I requested earlier (attached), I have another question for you.

I cannot find the information on subset analysis comparing the sexes with pooled data of studies 016 and 017. Similar to the Table you have on vol 16, page 103. Table 8.7.6.1 for age subgroups, I would need one for the sexes where the comparison between males and females can be displayed with p-values. I looked at the submission of 3/7/00, and this information is also not there. Could you give me this Table at your earliest convenience? If already submitted, please indicate location.

Allergan Response:

Table **8.7.6.1.2** on the following page presents the statistical results of the comparison between males and females within each treatment group. Comparison between males and females were performed using logistic regression using the following model:

Clinical success = sex + study + sex **x** study

Where:

Clinical success = yes or no

Sex = female or male
Study = 16C or 17C

Comparison between males and females within the Tazarotene 0.1% group show no significant differences. Within the Tazarotene 0.05% group, it appears that the clinical success rate for the female group is significantly higher than that of the male group. One may quickly conclude that Tazarotene 0.5% works better in females than in males. However, the result is the same for the Vehicle group in that the success rate of the female group is significantly higher than the male group. Therefore, the conclusion that Tazarotene 0.05% works better in females is spurious. The reason for the rates being different may be due to other reasons (i.e. females are more attentive to dermatological problems than males).

In addition, an analysis was done employing the model:

Clinical success = sex + drug + sex **x** drug

(There were significant drug and sex effects ($P < 0.001$), but there was no significant drug-by-sex interaction ($p = 0.547$).)

Table 8.7.6.1.2 Clinical Success[a] at Week 12 in the Phase 3 Studies Pooled

Sex Category	Tazarotene 0.1% N = 432	Tazarotene 0.05% N = 428	Total Tazarotene N = 860	Vehicle N = 443
Female	79/161 (49.1%)	75/150 (50.0%)	154/311 (49.5%)	55/176 (31.3%)
Male	115/271 (42.4%)	101/278 (36.3%)	216/549 (39.3%)	57/267 (21.4%)
P-Value[b]	0.159	0.006	0.004	0.021

a Clinical success rates based upon an overall lesional assessment of none, minimal, or mild.
b Comparison of female patients vs male patients based on logistic regression for 2 x 2 tables; there were no significant sex category-by-study-interactions.

FDA Question from April 28 E-mail

I am sorry to be a nuisance to you. There is something between the Tables on patient disposition (section 14.1 Table 2) and drug exposure (section 14.3 Table 43) in studies 016C and 017C that I don't understand. I would appreciate it if you could explain to me those differences between the number of completed patients and number of patients who were exposed for at least 8 weeks, specifically those in the tazarotene 0.1% group. According to the protocol (section 8.6.2. for 016C; I believe 017 has the same), a completed patient is one who has not been discontinued.

There are more completed patients in the disposition Tables (section 14.1 Table 2) than those who used drug for at least 8 weeks (section 14.3 Table 43). For instance, in 016C, in the tazarotene 0.1% group, 145 completed while 142 used drug for at least 8 weeks. Therefore, there are 3 who completed (NOT discontinued) without using drug for at least 8 weeks. Who are these 3 and why?

In 017C, 160 completed while 141 used drug for at least 8 weeks. Therefore, there are 19 who completed (NOT discontinued) without using drug for at least 8 weeks. Who are these 19 and why?

I would appreciate if you could clarify this dilemma for me.

Allergan Response:

The drug exposure tables in section 14.3 (Table 43 for the 016C study and Table 27 for the 017C study) were programmed to show the number of patients in each of the specified time intervals (i.e. at least 1 week, at least 2 weeks, etc.) based on the actual date of each visit.

However, by doing so, if a patient who completed the study at Week 12 had a visit date resulting in 55 days of exposure for the Week 8 visit, this patient's exposure was not included in the "at least 8 Weeks" interval but in the the "at least 4 Weeks" category; and since the patient completed the study at Week 12, he would also be counted in the at "least 12 Week interval."

Attached on the following page are two new drug exposure tables (Table 43 for the 016C study and Table 27 for the 017C study) that represent each patient by their actual exposure time. In the analysis, each patient's drug exposure time in weeks was calculated as *date of last dose* minus *date of first dose* +1. Therefore, a patient is represented in all duration intervals up to and including the interval category of the treatment duration.

Table 44
Patient Drug Exposure by Treatment Duration

	Taz 0.1% (N=221) Yes / Total[a] (%)	Taz 0.05% (N=218) Yes / Total[a] (%)	Vehicle (N=229) Yes / Total[a] (%)	Total (N=668) Yes / Total[a] (%)
Week 0 [a]	221(100.0%)	218(100.0%)	229(100.0%)	668(100.0%)
At Least 1 Week	214(96.8%)	213(97.7%)	219(95.6%)	646(96.7%)
At Least 2 Weeks	201(91.0%)	201(92.2%)	207(90.4%)	609(91.2%)
At Least 4 Weeks	186(84.2%)	186(85.3%)	195(85.2%)	567(84.9%)
At Least 8 Weeks	153(69.2%)	155(71.1%)	169(73.8%)	477(71.4%)
At Least 12 Weeks	131(59.3%)	106(48.6%)	145(63.3%)	382(57.2%)
At Least 14 Weeks	6(2.7%)	7(3.2%)	13(5.7%)	26(3.9%)

[a] Or at least 1 day.

/bostat/wong_ly/190168016c/drug_exp.sas/ 01MAY00

Table 27
Patient Drug Exposure by Treatment Duration

	Taz 0.1% (N=211) Yes / Total[a] (%)	Taz 0.05% (N=210) Yes / Total[a] (%)	Vehicle (N=214) Yes / Total[a] (%)	Total (N=635) Yes / Total[a] (%)
Week 0 [a]	211(100.0%)	210(100.0%)	214(100.0%)	635(100.0%)
At Least 1 Week	205(97.2%)	200(95.2%)	204(95.3%)	609(95.9%)
At Least 2 Weeks	196(92.9%)	193(91.9%)	194(90.7%)	583(91.8%)
At Least 4 Weeks	183(86.7%)	181(86.2%)	187(87.4%)	551(86.8%)
At Least 8 Weeks	169(80.1%)	158(75.2%)	175(81.8%)	502(79.1%)
At Least 12 Weeks	149(70.6%)	127(60.5%)	146(68.2%)	422(66.5%)
At Least 14 Weeks	8(3.8%)	10(4.8%)	9(4.2%)	27(4.3%)

[a] Or at least 1 day.

/bostat/wong_ly/190168017c/drug_exp.sas/ 01MAY00

We ask that these responses be reviewed and filed to NDA 21-184, TAZORAC® Cream. Should you have any further questions or require additional information, please call me at 714.246.4292 or Thomas Walton at 714.246.4470, Pacific Time.

Sincerely.

T. A. Rumbaugh M.D.

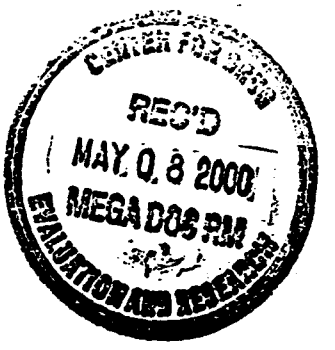
Trudy A. Rumbaugh, MD
Director.
Global Regulatory Affairs, Retinoids

TR:tww

May 5, 2000

NDA [illegible] AMENDMENT

Jonathan Wilkin, MD
Director,
Division of Dermatologic and Dental Drug Products
HFD-540/Room N115
Center for Drug Evaluation and Research
Food and Drug Administration
9201 Corporate Blvd., Building 2
Rockville, MD 20850



REF: TAZORAC® (tazarotene topical cream) 0.05%, 0.1%
NDA 21-184
Response to FDA Fax of April 25, 2000 (BioPharm Comments)

BB

Dear Doctor Wilkin:

Allergan is amending the above-referenced NDA with a response to the fax (dated March 13, 2000) with BioPharm comments received by Allergan on April 25, 2000.

FDA Comment

1.) Please clarify the exposure time with Tazorac cream in the studies PK-99-044, PK-99-060 &PK-099-085.

Allergan Response

a. For all patients with therapeutic drug monitoring (TDM) data from Study PK-99-044 (PK-99-044 is the PK report for clinical Study **190168-016C**), the time from the last dose to the trough level blood sampling is listed in Table 1 (refer to header "last dose to trough [a]"). Note that the study protocol did not specify requirements regarding bathing/showering during this period of time. General bathing/showering guidelines outlined in the protocol were related to the non-TDM portion of the study (i.e., "If patients bathe or shower in the evening, they will be instructed to apply the study medication after they have allowed their skin to dry").

   For all patients with TDM data from Study PK-99-044, the study medication "exposure" time, defined as the difference between the time of dosing at the clinic and the time of subsequent blood sampling is listed also in Table 1 (refer to header "exposure time [b]"). Patients were instructed not to wash or shower until after the blood collection was performed.

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b. For all patients with TDM data from study PK-99-060 (PK-99-060 is the PK report for clinical Study **190168-017C**), the time from the last dose to the trough level blood sampling is listed in Table 2 (refer to header "last dose to trough [a]"). Note that the study protocol did not specify requirements regarding bathing/showering during this exposure time. General bathing/showering guidelines outlined in the protocol were related to the non-TDM portion of the study (i.e., "If patients bathe or shower in the evening, they will be instructed to apply the study medication after they have allowed their skin to dry.").

   For all patients with TDM data from Study PK-99-060, study medication "exposure" time, defined as the difference between the time of dosing at the clinic and the time of subsequent blood sampling is listed in Table 2 (refer to header "exposure time [b]"). Patients were instructed not to wash or shower until after the blood collection was performed.

c. For study PK-099-085 (PK-99-085 is the PK report for clinical Study **190168-023C**), all patients were instructed to bathe/shower 12 hours after application of tazarotene cream. Therefore, the exposure time for all patients participating in this study was 12 hours.

FDA Comment

2.) ***Please submit information on how the cream was applied and how & when it was removed from the patients.***

Allergan Response

a. For studies PK-99-044 and PK-99-060 (PK-99-044 and PK-99-060 are the PK reports for clinical studies 190168-016C and 190168-017C respectively), the application procedure of study medication at the clinic was as follows:
   (1) patients were given a tube of study medication that had been pre-weighed by study personnel at the site
   (2) patients were asked to apply the study medication as they normally would
   (3) application of the study medication was witnessed by study personnel and the time of application noted
   (4) the tube of study medication was re-weighed by study personnel at the site
   (5) patients were instructed not to wash or shower until after their blood sample had been collected

(6) patients were instructed to return to the site approximately 3 to 10 hours later on the same day for collection of their blood sample, the time of which was noted.
(7) patients were instructed to resume their application of the study medication the following evening.

As stated previously, specific requirements regarding bathing/showering prior to the "trough" blood draw was not included in the protocol. General bathing/showering guidelines outlined in the protocol were related to application of study medication during the non-TDM portion of the study (i.e., "If patients bathe or shower in the evening, they will be instructed to apply the study medication after they have allowed their skin to dry.").

b. For Study PK-099-085 (PK-99-085 is the PK report for clinical Study **190168-023C**), application of tazarotene cream was conducted by site personnel, as described under Section 7.1.2 (Instructions for use and administration) of the Protocol 190168-023C (original NDA 21-184, Volume 12, Pages 266-267). Patients were instructed to bathe or shower 12 hours after tazarotene cream application. For your convenience, the relevant pages of the NDA 21-184 are attached following this cover memo.

3.) If you could submit this information within one week via fax and then formally submit it to Division File.

Per my voice mail update to Kalyani Bhatt of your Division on May 4, 2000, we have compiled the requested data diligently in the earliest possible manner.

Should you have any further questions or require additional information, please call me at 714.246.4292 or Thomas Walton at 714.246.4470, Pacific Time.

Sincerely,

Trudy A. Rumbaugh, MD
Director,
Global Regulatory Affairs, Retinoids

TR/sm

DEPARTMENT OF HEALTH & HUMAN SERVICES

Blatt

Food and Drug Administration
Rockville MD 20857

MAY 10 2000

Steven E. Kempers, M..D.
7502 University Avenue, N.E.
Fridley, Minnesota 55432

Dear Dr. Kempers:

Between February 2 and 11, 2000, Ms. Jennifer A. L. Vollom, representing the Food and Drug Administration (FDA), met with your staff to review your conduct of a clinical study (protocol #190168-017C-03) of the investigational drug Tazorac (tazarotene topical cream 0.05% and 0.1%), performed for Allergan. This inspection is a part of FDA's Bioresearch Monitoring Program, which includes inspections designed to validate clinical studies on which drug approval may be based and to assure that the rights and welfare of the human subjects of those studies have been protected.

From our evaluation of the inspection report and the documents submitted with that report we conclude that you adhered to all pertinent federal regulations and/or good clinical investigational practices governing your conduct of clinical investigations and the protection of human subjects.

We appreciate the cooperation shown Investigator Vollom during the inspection. Should you have any questions or concerns about any aspect of the clinical testing of investigational drugs, please contact me at (301)594-1032.

Sincerely yours,

/S/

Antoine El-Hage, Ph.D.
Branch Chief
Good Clinical Practice II, HFD-47
Division of Scientific Investigations
Office of Medical Policy
Center for Drug Evaluation and Research
7520 Standish Place
Rockville, MD 20855

FN: 3000284846

Field Classification: NAI

Headquarters Classification:
__X__ 1) NAI
_____ 2) VAI-no response required
_____ 3) VAI-response requested

If Headquarters classification is a different classification, explain why:

cc:
HFA-224
HFD-540 Review Div. Dir.
HFD-540/ MO/Ko
HFD-540/ PM/Bhatt
HFD-540/Doc. Rm. NDA # 21-184
HFD-45 r/f
HFD-47 c/r/s GCP file# 10007
HFD-47/Carreras
HFD-47/Currier
HFR-CE860/Bigham
HFR-CE850/Matson
HER-CE850/Vollom

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Note to Rev. Div. M.O.

ERGAN

ont Drive P.O. Box 19534, Irvine, California USA 92623-9534 Telephone: (714) 246-4500 Website: www.allergan.com

Appendix 1

190168-002

March 22, 2000

NDA ORIG AMENDMENT

Bm

Jonathan Wilkin, MD
Director,
Division of Dermatologic and Dental Drug Products
HFD-540/Room N115
Center for Drug Evaluation and Research
Food and Drug Administration
9201 Corporate Blvd., Building 2
Rockville, MD 20850

REF: TAZORAC® (tazarotene topical cream) 0.05%, 0.1%
NDA 21-184
Response to Fax of February 8, 2000

Dear Doctor Wilkin:

Allergan is amending the above-referenced NDA with adverse event information as requested your Clinical comments fax.

FDA Comment

1. *In the pre-NDA minutes (the meeting dated 6/14/99), the Sponsor has been advised (Clinical Item 1) the following:*

- *"All safety data must be presented, including postmarketing data for marketed formulations, data from studies on indications not sought and on formulations not marketed, and data from on-going studies not yet completed (domestic and foreign)."*

The Integrated Summary of Safety gave postmarketing data of tazarotene gels up to 7/15/99 only with incidence of the most common events. The Applicant needs to –

a) *clarify whether the information is from US sources or ALL sources;*
b) *provide incidence of death, serious adverse events or discontinuations due to adverse events; and*
c) *provide incidence of pregnancies and outcomes of pregnancies encountered in users.*
d) *summarize safety data from postmarketing studies (e.g., summary tables on the safety data from the long list of studies in the annual reports of NDA 20-600 would be appropriate)*

LERGAN

Irvine, P.O. Box 19534, Irvine, California, USA 92623-9534 Telephone: (714) 246-4500 Website: www.allergan.com

March 7, 2000

NDA CORRESPONDENCE

APR 10 2000

FOOD AND DRUG RESEARCH

Jonathan Wilkin, MD
Director,
Division of Dermatologic and Dental Drug Products
HFD-540/Room N115
Center for Drug Evaluation and Research
Food and Drug Administration
9201 Corporate Blvd., Building 2
Rockville, MD 20850

BM

REF: TAZORAC® (tazarotene topical cream) 0.05%, 0.1%
NDA 21-184
Response to FDA Fax of March 13, 2000

Dear Doctor Wilkin:

Allergan is amending the above-referenced NDA with a response to the fax received with clinical comments on March 13, 2000.

The response is organized by each of the four clinical comments received.

Should you have any further questions or require additional information, please call me at 714.246.4292 or Thomas Walton at 714.246.4470, Pacific Time.

Sincerely,

T. Rumbaugh

Trudy A. Rumbaugh, MD
Director,
Global Regulatory Affairs, Retinoids

TR/tww

ORIGINAL

Dupont Drive P.O. Box 19534, Irvine California USA 92623-9534 Telephone (714) 246-4500 Website: www.allergan.com

March 7, 2000

NDA ORIG AMENDMENT

Jonathan Wilkin, MD
Director,
Division of Dermatologic and Dental Drug Products
HFD-540/Room N115
Center for Drug Evaluation and Research
Food and Drug Administration
9201 Corporate Blvd., Building 2
Rockville, MD 20850

BC

REF: TAZORAC® (tazarotene topical cream) 0.05%, 0.1%
NDA 21-184/Chemistry, Manufacturing and Controls (CMC) Amendment
Updated Stability Report (24-months) for Tazarotene Cream 0.05%, 0.1%

Dear Doctor Wilkin:

Allergan is amending the above-referenced NDA with a CMC amendment consisting of an updated stability report extending the expiry date to — based on this report which follows tazarotene cream for up to —

The original NDA (Volume 3, Page 004) contained a stability report with up to 18-months of stability data and a projected expiry date of —

As only the stability data from 18-months to 24-months is new, Allergan does not believe this amendment would be considered a major amendment necessitating a change to the User Fee Action Date. Should your Division make a determination otherwise, *Allergan will withdraw the amendment; preserving the current User Fee Action Date.*

We ask that this stability update be reviewed and filed to NDA 21-184, TAZORAC® Cream. Should you have any questions or require any further information, please call me at 714.246.4292 or Thomas Walton at 714.246.4470, Pacific Time.

Sincerely,

T. Rumbaugh

Trudy A. Rumbaugh, MD
Director,
Global Regulatory Affairs, Retinoids

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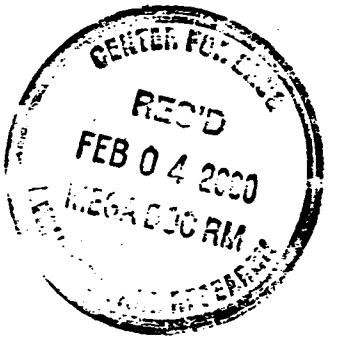
ALLERGAN

2525 Dupont Drive, P.O. Box 19534, Irvine, California, USA 92623-9534 Telephone: (714) 246-4500 Website: www.allergan.com

February 3, 2000

Jonathan Wilkin, MD
Director,
Division of Dermatologic and Dental Drug Products
HFD-540/Room N115
Center for Drug Evaluation and Research
Food and Drug Administration
9201 Corporate Blvd., Building 2
Rockville, MD 20850



REF: Tazorac® (tazarotene topical cream) 0.05%, 0.1%
NDA 21-184/120 Day Safety Update

Dear Doctor Wilkin:

Allergan is amending the above-referenced New Drug Application with the 120 Day Safety Update according to 21 CFR 314.50(d)(5)(vi)(b). Also, we are including information as was agreed between Allergan and FDA at the preNDA Meeting of June 14, 1999. The following information is included in this safety update:

Data required by 21 CFR 314.50(d)(5)(vi)(b):

- Case Report Forms for patients who discontinued due to an adverse event or death.

Data agreed to be included in the Safety Update from the preNDA Meeting:

- Re-challenge in the human photoallergy study with UVA irradiation, Study 190168-032C
- Provide plasma sample analysis from human pharmacokinetic study 190168-024C.

On the basis of this information, there will be no change to either the Integrated Summary of Safety or to the contraindications, warnings, precautions and adverse events as described in the draft labeling and as provided in the original NDA.

Division of Dermatologic and Dental Drug Products
Center for Drug Evaluation and Research
Food and Drug Administration
5600 Fishers Lane, HFD-540
Rockville, MD 20857

FACSIMILE TRANSMISSION RECORD

DATE: 11/18/99 Pages (including cover) 5 pages

TO: Paul Stinavase

COMPANY: FDA HFD-160

ADDRESS:

FAX PHONE#: 301 ~~443-9281~~ 827-3084 Our Fax # (301) 827-2075

Voice # (301) 827-2020

MESSAGE:

Mr. Stinavase,

You will receive your own desk copy.

Hope this information is enough.

Thanks,

/S/

NOTE: We are providing the attached information via telephone facsimile for your convenience. This material should be viewed as unofficial correspondence. Please feel free to contact me if you have any questions regarding the contents of this transmission.

FROM: /S/

TITLE: Project Manager

TELEPHONE: 301 827-2049

Table 4A.3.6.3-2 Product Tests and Specifications for Tazarotene Topical Cream 0.05%

Test	Release Specification	Regulatory Specification	Method
Tazarotene Concentration			
Tazarotene Identification[1]			
AGN 190832			
Total Tazarotene Related Substances[2]			
Content Uniformity			
Benzyl Alcohol			
Sodium Thiosulfate			
Edetate Disodium			
Viscosity			
Physical Appearance			
pH			
Microbial Limits Test		Not applicable	USP
Preservative Effectiveness Test		Bacteria show reduction of 1 log/7 days and 3 log/14 days contact plus fungistasis at 14 and 28 days	USP
Fill Weight			
Package Integrity			

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ON ORIGINAL

4A.3.6.4 Rationale for Drug Product Specifications

The above listed specifications are those necessary for the product to be a safe, stable and efficacious dosage form.

Active Ingredient Concentration

The specifications on the active ensure appropriate dosing levels.

The specification on this degradation product ensures that the manufacturing process is well controlled.

Total Tazarotene Related Substances

This specification includes all specified and identified tazarotene degradation products. These are comprised of the sum of

One noteworthy difference in specifications for tazarotene cream relative to Tazorac® Gel is the absence of a specification on

It is not observed to form at sufficient concentrations to require a discrete separate specification; as such it is included in the specification for all tazarotene related substances.

Content Uniformity

This specification ensures that the drug product remains homogeneous throughout its shelf-life.

Benzyl Alcohol

This specification ensures that the manufacturing process is well-controlled and that the product has adequate antimicrobial preservation.

Sodium Thiosulfate

This specification ensures manufacturing consistency and adequate antioxidant preservation of the product. The release specification ensures that sufficient antioxidant was present at time of manufacture to remove any oxidizing species carried by any of the excipient ingredients. No shelf specification is warranted since antioxidants are expected to be consumed over time.

Edetate Disodium

This specification ensures manufacturing consistency. The release specification ensures that sufficient chelating agent was present at time of manufacture to complex any multivalent cations carried by any of the excipient ingredients. No shelf specification is warranted since chelating agents are not consumed over time.

pH and Viscosity

The active ingredient is an ester, and the formulation viscosity is adjusted with carbomer. Therefore, the pH of the final product not only effects the viscosity of the cream through modification of the carbomer, but also could potentially affect the hydrolytic stability of the product. The pH range was set such that the carbomer would be an efficient viscosity enhancer, and minimize any potential hydrolytic decomposition. The pH range is also relatively close to that of the skin thereby reducing potential irritation effect.

Physical Appearance

This specification ensures that there is no phase separation of the tazarotene cream emulsion.

Microbial Limits Test

This specification ensures the microbial quality of the finished product with the absence of objectionable organisms.

Preservative Effectiveness Test

This specification ensures the adequate antimicrobial preservation of the product.

4A.3.6.5 Description and Rationale of Analytical Tests for Drug Product

The standard tests generally performed to control the quality of dermatological dosage form are physical appearance, pH, viscosity, content uniformity, active ingredient concentration, related substance(s) concentration, preservative(s) concentration, microbial limits, and preservative effectiveness. Each of these tests has been validated to meet compendial requirements for the tazarotene topical cream such that accurate and reproducible results are obtained.

Detailed descriptions of each analytical method with their respective validation data are provided in Appendix 4A.6.4 vol 2 p. 148 with the exception of the Physical Appearance,

DEPARTMENT OF HEALTH & HUMAN SERVICES Public Health Service

Food and Drug Administration
Rockville MD 20857

NDA 21-184

OCT 7 1999

Allergan, Inc.
Attention: Trudy A. Rumbaugh, MD
Director, Global Regulatory Affairs
2525 Dupont Drive
PO Box 19534
Irvine, CA 92623-9534

Dear Dr. Rumbaugh:

We have received your new drug application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for the following:

Name of Drug Product: Tazorac (tazarotene 0.05%/0.1%) Topical Cream

Therapeutic Classification: Standard (S)

Date of Application: September 30, 1999

Date of Receipt: September 30, 1999

Our Reference Number: NDA 21-184

Unless we notify you within 60 days of our receipt date that the application is not sufficiently complete to permit a substantive review, this application will be filed under section 505(b) of the Act on November 29, 1999 in accordance with 21 CFR 314.101(a). If the application is filed, the primary user fee goal date will be July 31, 2000 and the secondary user fee goal date will be September 30, 2000.

Be advised that, as of April 1, 1999, all applications for new active ingredients, new dosage forms, new indications, new routes of administration, and new dosing regimens are required to contain an assessment of the safety and effectiveness of the product in pediatric patients unless this requirement is waived or deferred (63 *FR* 66632). If you have not already fulfilled the requirements of 21 CFR 314.55 (or 601.27), please submit your plans for pediatric drug development within 120 days from the date of this letter unless you believe a waiver is appropriate. Within 120 days of receipt of your pediatric drug development plan, we will notify you of the pediatric studies that are required under section 21 CFR 314.55.

If you believe that this drug qualifies for a waiver of the study of the pediatric study requirement, you should submit a request for a waiver with supporting information and documentation in accordance with the provisions of 21 CFR 314.55 within 60 days from the date of this letter. We will notify you within 120 days of receipt of your response whether a waiver is granted. If a waiver is not granted, we will ask you to submit your pediatric drug development plans within 120 days from the date of denial of the waiver.

Pediatric studies conducted under the terms of section 505A of the Federal Food, Drug, and Cosmetic Act may result in additional marketing exclusivity for certain products (pediatric exclusivity). You should refer to the *Guidance for Industry on Qualifying for Pediatric Exclusivity* (available on our web site at www.fda.gov.cder/pediatric) for details. If you wish to qualify for pediatric exclusivity you should submit a "Proposed Pediatric Study Request" (PPSR) in addition to your plans for pediatric drug development described above. We recommend that you submit a Proposed Pediatric Study Request within 120 days from the date of this letter. If you are unable to meet this time frame but are interested in pediatric exclusivity, please notify the division in writing. FDA generally will not accept studies submitted to an NDA before issuance of a Written Request as responsive to a Written Request. Sponsors should obtain a Written Request before submitting pediatric studies to an NDA. If you do not submit a PPSR or indicate that you are interested in pediatric exclusivity, we will proceed with the pediatric drug development plan that you submit, and notify you of the pediatric studies that are required under section 21 CFR 314.55. Please note that satisfaction of the requirements in 21 CFR 314.55 alone may not qualify you for pediatric exclusivity. FDA does not necessarily ask a sponsor to complete the same scope of studies to qualify for pediatric exclusivity as it does to fulfill the requirements of the pediatric rule.

Please cite the NDA number listed above at the top of the first page of any communications concerning this application. All communications concerning this NDA should be addressed as follows:

U.S. Postal Service:

Food and Drug Administration
Center for Drug Evaluation and Research
Division of Dermatologic and Dental Drug Products, HFD-540
5600 Fishers Lane
Rockville, Maryland 20857

Courier/Overnight Mail:

Food and Drug Administration
Center for Drug Evaluation and Research
Division of Dermatologic and Dental Drug Products, HFD-540
9201 Corporate Blvd.
Rockville, Maryland 20850-3202

If you have any questions, contact Kalyani Bhatt, Project Manager, at 301-827-2020.

Sincerely,

/S/

Mary Jean Kozma-Fornaro
Supervisor, Project Management Staff
Division of Dermatologic and Dental Drug Products
Office of Drug Evaluation V
Center for Drug Evaluation and Research

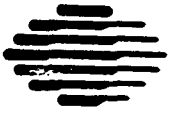
cc:
Archival NDA 21-184
HFD-540/Div. Files
HFD-540/K.Bhatt
HFD-540/S.Walker
HFD-540/A.Jacobs
HFD-540/W.DeCamp
DISTRICT OFFICE

Drafted by: /smc/October 5, 1999
filename: N21184.ACK

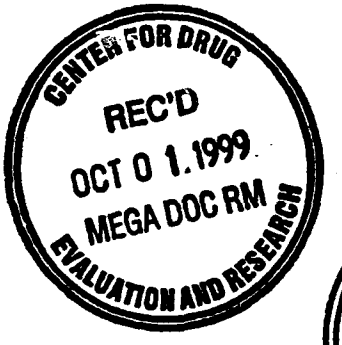
ACKNOWLEDGEMENT (AC)

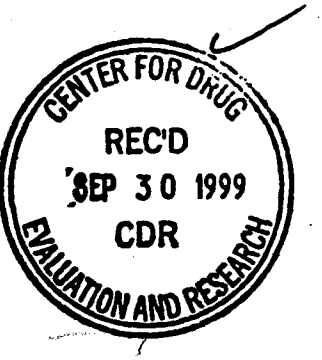
ALLERGAN

2525 Dupont Drive, P.O. Box 19534, Irvine, California, USA 92623-9534 Telephone: (714) 246-4500 Website: www.allergan.com



September 30, 1999





Food and Drug Administration
Document and Records Section
CDER Central Document Room
12420 Parklawn Drive
Rockville, MD 20852

REF: Tazorac® (tazarotene topical cream) 0.05%, 0.1%
Original NDA 21-184

User Fee Number 3797

Dear Sir or Madam:

Allergan is submitting an original New Drug Application in accordance with the relevant portions of 21 CFR 314.50, 21 CFR 314.440, and 21 CFR Part 11, and also in accordance with the guidance provided at the PreNDA Meeting of June 14, 1999 between Allergan and the Division of Dermatologic and Dental Drugs Products. We are seeking an indication for the treatment of plaque psoriasis for Tazorac® (tazarotene topical cream) 0.05%, 0.1% which is a line extension of the previously approved Tazorac® (tazarotene topical gel) 0.05%, 0.1%.

The key trials in support of this application are the phase 3 studies conducted in the United States, Studies 190168-016C and 190168-017C. These were both multicenter, double-blind, randomized, vehicle-controlled studies to evaluate the safety and efficacy of tazarotene creams 0.1% and 0.05% applied once daily for 12 weeks in patients with plaque psoriasis. (Study 190168-016C also included a 12-week post-treatment follow-up period). Both tazarotene creams 0.1% and 0.05% have demonstrated significant efficacy, together with acceptable tolerability. Adverse effects were evidenced mainly as local irritation, a profile similar to that of tazarotene in the approved gel formulation. Although tazarotene cream 0.1% was generally more efficacious than 0.05%, it was associated with more local irritation. This juxtaposition of effectiveness and local irritation potential with the 2 concentrations of tazarotene offers physicians and patients substantial flexibility in treating psoriasis.

This application consists of both an Archival and Review copy. All portions of the submission are presented only in paper format except for Item 11 (case report tabulations) which is presented only in electronic format in accordance with 21 CFR Part 11. Please see *Attachment 1* for a description of the electronic submission and verification that the submission is virus free. The CD containing the electronic portion are located in a sleeve in the front of Volume 1 in both the Archival and official Review copy.

acceptable as RA.

Twenty additional paper copies of Volume 1, which include the Master Index and Certifications (Section 1), Labeling (Section 2) and Summary (Section 3), have also been provided as an aid to the reviewers. A Field copy of the Chemistry, Manufacturing and Controls Section (Section 4A) and Volume 1 (containing Sections 1, 2, and 3), have been forwarded to both the FDA's Dallas and Los Angeles District Offices. In addition to the Archival copy of the Methods Validation Section (Section 4C), three paper review copies have also been included in the original submission. Please refer to *Attachment 2* to see a table summarizing this distribution of copies. Samples of the New Drug Product will be submitted to the appropriate FDA testing facility upon receiving the request and instructions from the agency. Allergan certifies that the Field copies are identical to the Archival and Review copies submitted herein.

In accordance with the Division of Dermatologic and Dental Drug Products' request, Allergan is certifying that all Allergan facilities utilized in the development, validation, manufacturing and quality assurance of Tazorac® Creams (Irvine, California; Waco, Texas; Westport, Ireland) are prepared for inspection.

The Active Pharmaceutical Ingredient, tazarotene, has been previously approved in NDA 20-600, Tazorac® (tazarotene topical gel) 0.05%, 0.1%, for the topical treatments of acne vulgaris (0.1%) and plaque psoriasis (0.05%, 0.1%).

We ask that this original NDA be recorded and forwarded to the Division of Dermatologic and Dental Drug Products for review. Should you require any additional information or have any questions, please call me at 714.246.4292 or Thomas Walton at 714.246.4470, Pacific Time.

Sincerely,

Trudy A. Rumbaugh, MD
Director,
Global Regulatory Affairs, Retinoids

TR/tww

cc: Frank Cross, Jr., MA, CDR,
Senior Regulatory Management Officer

DEPARTMENT OF HEALTH AND HUMAN SERVICES
FOOD AND DRUG ADMINISTRATION

APPLICATION TO MARKET A NEW DRUG, BIOLOGIC, OR AN ANTIBIOTIC DRUG FOR HUMAN USE

(Title 21, Code of Federal Regulations 314 & 601)

Form Approved: OMB No. 0910-0338
Expiration Date: April 30, 2000
See OMB Statement on last page.

FOR FDA USE ONLY

APPLICATION NUMBER

APPLICANT INFORMATION

NAME OF APPLICANT	DATE OF SUBMISSION
Allergan, Inc.	9/30/99
TELEPHONE NO. *(Include Area Code)* 800-347-4500	**FACSIMILE (FAX) Number** *(Include Area Code)* 714-246-4272

APPLICANT ADDRESS *(Number, Street, City, State, Country, ZIP Code or Mail Code, and U.S. License number if previously issued):*
2525 Dupont Drive
P.O. Box 19534
Irvine, CA 92623-9534

AUTHORIZED U.S. AGENT NAME & ADDRESS (Number, Street, City, State, ZIP Code, telephone & FAX number) IF APPLICABLE

PRODUCT DESCRIPTION

NEW DRUG OR ANTIBIOTIC APPLICATION NUMBER, OR BIOLOGICS LICENSE APPLICATION NUMBER (if known) NDA 21-184

ESTABLISHED NAME *(e.g., Proper name, USP/USAN name)*	PROPRIETARY NAME *(trade name)* IF ANY
Tazarotene (USAN)	Tazo[illegible]

CHEMICAL/BIOCHEMICAL/BLOOD PRODUCT NAME *(if any)*	CODE NAME *(if any)*
Ethyl 6-[(4,4-dimethylthiochroman-6-yl)ethynyl]nicotinate	AGN 190168

DOSAGE FORM:	STRENGTHS:	ROUTE OF ADMINISTRATION:
Topical Cream	0.05% 0.1%	Topical

(PROPOSED) INDICATION(S) FOR USE:
Once daily treatment of plaque psoriasis.

APPLICATION INFORMATION

APPLICATION TYPE (check one)
■ NEW DRUG APPLICATION (21 CFR 314.50) □ ABBREVIATED APPLICATION (ANDA, AADA, 21 CFR 314.94)
□ BIOLOGICS LICENSE APPLICATION (21 CFR part 601)

IF AN NDA, IDENTIFY THE APPROPRIATE TYPE ■ 505 (b) (1) □ 505 (b) (2) □ 507

IF AN ANDA, OR AADA, IDENTIFY THE REFERENCE LISTED DRUG PRODUCT THAT IS THE BASIS FOR THE SUBMISSION

Name of Drug	Holder of Approved Application

TYPE OF SUBMISSION (check one)
■ ORIGINAL APPLICATION □ AMENDMENT TO A PENDING APPLICATION □ RESUBMISSION
□ PRESUBMISSION □ ANNUAL REPORT □ ESTABLISHMENT DESCRIPTION SUPPLEMENT □ SUPAC SUPPLEMENT
□ EFFICACY SUPPLEMENT □ LABELING SUPPLEMENT □ CHEMISTRY MANUFACTURING AND CONTROLS SUPPLEMENT □ OTHER

REASON FOR SUBMISSION Request for marketing approval.

PROPOSED MARKETING STATUS (check one) ■ PRESCRIPTION PRODUCT (Rx) □ OVER THE COUNTER PRODUCT (OTC)

NUMBER OF VOLUMES SUBMITTED 170 | **THIS APPLICATION IS** □ PAPER ■ PAPER AND ELECTRONIC □ ELECTRONIC

ESTABLISHMENT INFORMATION

Provide locations of all manufacturing, packaging and control sites for drug substance and drug product (continuation sheets may be used if necessary). Include name, address, contact, telephone number, registration number (CFN), DMF number, and manufacturing steps and/or type of testing (e.g., Final dosage form, Stability testing) conducted at the site. Please indicate whether the site is ready for inspection or, if not, when it will be ready.

Refer to attachment.

Cross References (list related License Applications, INDs, NDAs, PMAs, 510(k)s, IDEs, BMFs, and DMFs referenced in the current application)

IND — Allergan, Inc. NDA 20-600 Allergan, Inc.

This application contains the following items: (Check all that apply)	
X	1. Index
X	2. Labeling (check one) ☒ Draft Labeling ☐ Final Printed Labeling
	3. Summary (21 CFR 314.50 (c))
X	4. Chemistry section
X	A. Chemistry, manufacturing, and controls information (e.g. 21 CFR 314.50 (d) (1), 21 CFR 601.2)
	B. Samples (21 CFR 314.50 (e) (1), 21 CFR 601.2 (a)) (Submit only upon FDA's request)
X	C. Methods validation package (e.g. 21 CFR 314.50 (e) (2) (i), 21 CFR 601.2)
X	5. Nonclinical pharmacology and toxicology section (e.g. 21 CFR 314.50 (d) (2), 21 CFR 601.2)
X	6. Human pharmacokinetics and bioavailability section (e.g. 21 CFR 314.50 (d) (3), 21 CFR 601.2)
X	7. Clinical Microbiology (e.g. 21 CFR 314.50 (d) (4))
X	8. Clinical data section (e.g. 21 CFR 314.50 (d) (5), 21 CFR 601.2)
X	9. Safety update report (e.g. 21 CFR 314.50 (d) (5) (vi) (b), 21 CFR 601.2)
X	10. Statistical section (e.g. 21 CFR 314.50 (d) (6), 21 CFR 601.2)
X	11. Case report tabulations (e.g. 21 CFR 314.50 (f) (1), 21 CFR 601.2)
X	12. Case report forms (e.g. 21 CFR 314.50 (f) (2), 21 CFR 601.2)
X	13. Patent information on any patent which claims the drug (21 U.S.C. 355 (b) or (c))
X	14. A patent certification with respect to any patent which claims the drug (21 U.S.C. 355 (b) (2) or (j) (2) (A))
	15. Establishment description (21 CFR Part 600, if applicable)
X	16. Debarment certification (FD&C Act 306 (k)(1))
	17. Field copy certification (21 CFR 314.5 (k) (3))
X	18. User Fee Cover Sheet (Form FDA 3397)
	19. OTHER (Specify)

CERTIFICATION

I agree to update this application with new safety information about the product that may reasonably affect the statement of contraindications, warnings, precautions, or adverse reactions in the draft labeling. I agree to submit safety update reports as provided for by regulation or as requested by FDA. If this application is approved, I agree to comply with all applicable laws and regulations that apply to approved applications, including, but not limited to the following:

1. Good manufacturing practice regulations in 21 CFR 210 and 211, 606, and/or 820.
2. Biological establishment standards in 21 CFR Part 600.
3. Labeling regulations in 21 CFR 201, 606, 610, 660 and/or 809.
4. In the case of a prescription drug or biological product, prescription drug advertising regulations in 21 CFR 202.
5. Regulations on making changes in applications in 21 CFR 314.70, 314.71, 314.72, 314.97, 314.99, and 601.12.
6. Regulations on reports in 21 CFR 314.80, 314.81, 600.80 and 600.81.
7. Local, state and Federal environmental impact laws.

If this application applies to a drug product that FDA has proposed for scheduling under the Controlled Substances Act, I agree not to market the product until the Drug Enforcement Administration makes a final scheduling decision.

The data and information in this submission have been reviewed and, to the best of my knowledge are certified to be true and accurate.

Warning: a willfully false statement is a criminal offense, U.S. Code, title 18, section 1001.

SIGNATURE OF RESPONSIBLE OFFICIAL OR AGENT	TYPED NAME AND TITLE	DATE
Trudy A. Rumbaugh	Trudy A. Rumbaugh, MD, Director, Global Regulatory Affairs	9-30-99

ADDRESS (Street, City State, and ZIP Code)	Telephone Number
2525 Dupont Drive, P.O. Box 19534, Irvine, CA 92623-9534	(714) 246-4292